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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,614	GOLZ ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,10-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 30 September 2009.

Claim Status

Claims 1-4, 6 and 9-17 are pending. Claims 5, 7-9 and 14 are cancelled. Claims 1 and 15 are amended. Claim 17 is newly submitted. Claims 1-4, 6, 10-13 and 15-17 are under current examination.

Priority

This application claims benefit as a 371 of PCT/EP03/13281 (filed 11/26/2003). The application also claims benefit from the foreign (German) patent application 10257354.9 (filed 12/9/2002). The instant application has been granted the benefit date, 9 December 2002, from the German application 10257354.9.

RESPONSE TO ARGUMENTS

35 USC § 112, first paragraph (written description)

The rejection of claims 1-4, 6, 10-13 and 15-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to the applicants arguments and/or claim amendments.

The applicant's arguments and claim amendments have been fully considered and are persuasive. The applicant has amended claims 1 and 15 by joining elements c)

and d) so that the claimed genus of nucleic acids is directed to: an isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule encoding a polypeptide having the amino acid sequence of SEQ ID NO:2;

b) a nucleic acid molecule comprising the sequence of SEQ ID NO:1;

c) a nucleic acid molecule which is at least 95% homologous to SEQ ID NO:1, whose complementary strand hybridizes under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1; and which encodes a fluorescent protein. Claim 15 also includes the limitations that the fluorescent protein has an excitation peak of about 475 nm and an emission peak of about 493 nm.

The examiner concludes that the applicant is in possession of the scope of the pending claims. The literal sequences SEQ ID NO:1 and 2 are free of the art. Therefore, there is no doubt that the applicant is in possession of Markush members a) and b). Furthermore, the limitation of Markush member c) directed to a nucleic acid molecule which is at least 95% homologous to SEQ ID NO:1, is free of the art. In combination with the hybridization limitations and the requirement that the protein is fluorescent, ensures that a certain amount of structural and functional relationship to SEQ ID NO:1 is maintained. As the sequence of SEQ ID NO:1 is novel and there seems to be no closely related art to SEQ ID NO:2 other than the Levine reference used to reject claims 6 and 17 (see below), the examiner concludes that the applicant is entitled to some breadth around the novel contribution to science. Therefore, the

examiner concludes that there is written description support in the specification, and in view of the numerous examples of fluorescent proteins known to the art, for the breadth of the instant claims.

Therefore, the examiner hereby withdraws the rejection of claims 1-4, 6, 10-13 and 15-16 under 35 U.S.C. 112, first paragraph (written description).

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Levine

Claim 6 remains rejected under 35 USC 102(b) as anticiapted by Levine et al (Compar. Biochem. Physiol. B, 1982. 72; 1:77-86).

Applicant's arguments (Remarks, pages 11-15) filed 30 September 2009 have been fully considered but are unpersuasive.

The applicant argues that the GFP taught by Levine is not the same as the fluorescent protein encoded by the polynucleotide of claim 1. The applicant argues that because claim 6 encompasses a genus of isolated proteins encoded by the genus of polynucleotides of claim 1, that the cited art does not teach all the limitations of the instant claim. The examiner finds this argument unpersuasive, since the cited reference does not need to teach the entire genus of molecules encompassed by claim 6.

According to the examiner's interpretation, Levine teaches at least one species of protein encompassed by the genus of protein described by claim 6.

The applicant suggests that the examiner's logic regarding inherency is flawed (Remarks, page 13). The applicant particularly argues that the examiner has not provided a factual basis or technical reason that the fluorescent protein of Levine is identical to the protein of claim 6. Contrary to the applicant's assertion, the examiner (in the Action filed 3/31/2009) has provided a basis in fact and/or technical reasoning to reasonably support the determinination that the allegedly inherent characteristic necessarily flow from the teachings of the appliced prior art. The examiner reiterates the reasons why he has come to the conclusion that the isolated protein of Levine is the same as the isolated protein of the instant invention:

Levine and the instant application isolated a green fluorescent protein from the same organism. Levine et al. isolate a green fluorescent protein from *Phialidium gregarium*. The organism *Phialidium gregarium* is sometimes referred to by the alternate name, *Clytia gregaria*. The applicant isolated a green fluorescent protein from *Clytia gregaria*.

The examiner has used the logical reasoning that "if the Levine protein is the same protein as that of claim 6, then Levine would inherently satisfy the sequence related claim language."

Levine isolated their GFP in 1982 using GFP using conventional protein purification methods. At the time Levine isolated their GFP, the molecular biological tools used by the applicant in 2002, were only beginning to be extensively utilized by

research laboratories. Levine does not characterize the properties of the GFP using molecular biological methods. Rather, Levine uses methods more common to the 1970s. It is on this basis that the examiner finds that the two proteins are the same. Without a laboratory and without samples of both the Levine GFP and instantly claimed GFP, the examiner cannot demonstrate exact sequence identity. Nevertheless, this sequence would be inherent, if the proteins are identical. See MPEP 2112 (*In re Best*).

The approximate molecular weight of the Levine GFP and the claimed GFP have approximately the same molecular weight. The applicant has indicated that Liu et al. ("Crystal structure of green fluorescent protein from *Clytia gregaria* at 1.55 Å resolution," Protein Data Bank entry 2HPW, deposited July 17, 2006) has determined that the *Clytia gregaria* GFP is 26,385.0 grams/mole (as determined by x-ray crystalography). The molecular weight of the Levine GFP was estimated to be 57,000 +/- 4% grams/mol (as determined by gel filtration). Levine discusses the variations between their methods and those of other laboratories when measuring the apparent molecular weights of other GFPs in the same paragraph as that revealing their estimation of P-GFP to be 57,000 +/- 4% grams/mol. The implication is that their measurement may not be completely accurate. In fact, Levine et al. suggest that the apparent molecular weights measured by gel filtration may vary by 20 to 50% (page 80, col.1, 2nd parag to col.2, top). In addition, the Levine GFP was isolated using native (non-denaturing) conditions. It is well known in the art that GFP dimerize under native conditions. Therefore, the estimated molecular weight of the Levine GFP is probably measuring a dimer. Accordingly, the estimated molecular weight a Levine GFP monomer is about

28,500 grams/mol. Considering the inaccuracies of the gel filtration method of determining molecular weight and the likelihood that Levine's measurements of their GFP was performed on a native dimer of GFP, the green fluorescent protein of Levine and the green fluorescent protein of the instant application have approximately the same molecular weight.

Emission spectra from Levine and Instant application provide data which seems to indicate that the respective protein have a similar emission spectra. The specification does not explicitly state what is the excitation and emission spectra for SEQ ID NO:2, but indicates that Figure 4 depicts the excitation of CGFP, while Figure 5 depicts the emission of CGFP (instant protein having the polypeptide sequence SEQ ID NO:2). The scale of instant Figures 4 and 5 permit only a rough estimation of the actual excitation maximum and emission maximums and shoulders. In the examiner's opinion, these data seem to be extremely close to the those provided by Levine. Levine states that "corrected fluorescence excitation spectrum for P-GFP shows a maximum at 487nm and a shoulder near 470nm (Fig.3). The emission spectrum, a mirror image of the excitation, has a maximum at 497nm and a broad shoulder in the 530-540nm range" (page 79, col.2). The applicant provides a comparison of the excitation and emission spectra for both SEQ ID NO:2 and P-GFP (Levine) in Schematic 1 (Remarks filed 2/14/2009, page 20). The applicant makes several conclusions based on the data shown in Schematic 1. The applicant and examiner disagree on the meaning of the subtle differences between the spectral data of the two proteins. Without a side-by-side comparison of the two proteins performed in the same experiment, it is difficult to

determine if the spectral data can confirm the existence of two different proteins. Levine compares their GFP to other GFP molecules isolated from other organisms (Fig.3, page 81). In this comparison, the examiner is able to easily distinguish the differences in excitation spectra of the three different GFPs depicted. As the information provided seems to indicate that the spectral data is quite similar, the Office concludes that these are, in fact, the same protein.

The applicant has raised the issue of the relative shape of the GFP excitation profiles of the Levine GFP and the claimed GFP. The excitation profile of instantly claimed SEQ ID NO:2 GFP clearly shows a double hump in Figure 4. The excitation profile of SEQ ID NO:2 was made from lysates of E.coli comprising plasmids carrying the SEQ ID NO:1 gene (Spec., page 19, Example 5). The excitation profile of the Levine GFP is in fact a "corrected fluorescence excitation spectrum" for Phailidium GFP, Aequorea GFP and Renilla GFP (Fig.3, page 81). None of these GFP show double humps. The state of the art (Roger Tsien. *Annu. Rev Biochem.* 1998. 67: 509-544) indicates, in the context of discussing GFP from *Aequorea victoria*, that most GFP molecules have double humped excitation peaks (page 525, lines 4-5). Since none of the GFP profiles shown in Levine, Fig.3 show this double humped excitation peak, despite the fact that both Aequorea GFP and Renilla GFP are known to normally show this shape, the examiner concludes that either the "correction" of Levine's methodology or some other effect in his method has masked one of the humps. So, despite the applicant's assertion that the single-peak excitation profile of the Levine GFP differentiates this protein from the claimed protein, the examiner finds this argument

unpersuasive. Therefore, the examiner concludes that the spectral characteristics of the Levine GFP and the instantly claimed GFP provide a suitable basis in face and/or technical reasoning that supports the determination that Levine inherently discloses the same green fluorescent protein as claimed.

Accordingly, the examiner hereby maintains rejection of claim 6 under 35 U.S.C. 102(b) as being anticipated by Levine et al (Compar. Biochem. Physiol. B, 1982. 72;1:77-86).

The examiner reiterates the pending rejection:

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Levine et al (Compar. Biochem. Physiol. B, 1982. 72;1:77-86). Claim 6 is directed to an isolated protein which is encoded by the nucleotide sequence of claim 1. Levine et al. isolated a green fluorescent protein from *Phialidium gregarium*. The organism *Phialidium gregarium* is sometimes referred to by the alternate name, *Clytia gregaria*. The applicant isolated a green fluorescent protein from *Clytia gregaria*. These are the same green fluorescent proteins. Accordingly, Levine et al. anticipated the instant claim.

Fraile-Ramos

The rejection of claim 14 under 102(b) as being anticipated by Fraile-Ramos et al. (Molecular Biology of the Cell. June 2001; 12: 1737-1749) is withdrawn in response to the applicant's claim amendments. The applicant has cancelled claim 14. Therefore, the rejection of this claim is moot. Accordingly, the examiner hereby

withdraws the rejection of claim 14 under 102(b) as being anticipated by Fraile-Ramos et al.

Tsien

Claim 15 remains rejected under 102(b) as being anticipated by Tsien et al. (US-5,777,079, published Jul. 7, 1998) for the reasons of record and the comments below.

The applicant's arguments and claim amendments have been fully considered but are unpersuasive.

The applicant has amended claim 15, combining elements of options c) and d). The previous anticipation rejection was based upon providing teachings which met the limitations of element c).

The applicant argues that as the previous anticipation rejection was based upon providing teachings in Tsien which met the limitations of element c) and the examiner did not explicitly indicate that Tsien satisfied the limitations of element d), that based upon the claim amendments, the cited art no longer anticipates the pending claim.

The examiner finds this argument unpersuasive. While it is true that the examiner only described how element c) anticipated the instant claim, the examiner interprets the new claim language as being satisfied by Tsien.

Therefore, the examiner hereby maintains the rejection of claim 15 under 35 U.S.C. 102(b) as being anticipated by Tsien.

The examiner reiterates the pending rejection:

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US-5,777,079, published Jul. 7, 1998).

Claim 15 is directed to an isolated nucleic acid molecules selected form the group consisting of:

a) a nucleic acid molecule encoding a polypeptide having the amino acid sequence of SEQ ID NO:2;

b) a nucleic acid molecule comprising the sequence of SEQ ID NO:1;

c) a nucleic acid molecule which is at least 95% homologous to SEQ ID NO:1 whose complementary strand hybridizes under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1, and encodes a fluorescent protein having an excitation peak of about 475 nm and an emission peak of about 493 nm.

The examiner interprets option c) of claim 15 as requiring (1) only a small region of the claimed nucleic acid molecule as being 95% homologous to SEQ ID NO:1; (2) the complementary strand of the nearly any nucleic acid molecule (especially those taught by Tsien which encode fluorescent proteins) as being able to hybridize under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1; and (3) the fluorescent proteins of Tsien (especially the mutant GFP which has an excitation peak of about 475 nm and an emission peak of about 493 nm) as encoding a fluorescent protein having an excitation peak of about 475 nm and an emission peak of about 493 nm.

Tsien et al. teach modifications of green fluorescent protein having markedly different excitation and emission spectra from wild type GFP (abstract). Furthermore, Tsien et al. teach a mutant GFP which has an excitation peak of about 475 nm and an emission peak of about 493 nm (See Fig.3a and Fig.3b). Tsien et al. teach the nucleic acid sequence which encodes the mutant GFP. Furthermore, the complementary strand of the Tsien nucleic acid would hybridize under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1. In addition, at least a portion of the Tsien mutant GFP is 95% homologous to SEQ ID NO:1, since the instant application teaches that the Tsien GFP is 44% homologous to the instantly claimed GFP. Additionally, the examiner interprets the phrase, "encodes a fluorescent protein" as referring to the nucleic acid molecule to which the claimed nucleic acid hybridizes (i.e., a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1).

Therefore, Tsien et al. anticipated the instant claim.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Levine

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Levine et al (Compar. Biochem. Physiol. B, 1982. 72;1:77-86).

Claim 17 is directed to an isolated protein comprising SEQ ID NO:2.

The instant specification teaches that the isolated protein of SEQ ID NO:2 is a Green Fluorescent Protein isolated from *Clytia gregaria*. Levine et al. isolated a green fluorescent protein from *Phialidium gregarium*. The organism *Phialidium gregarium* is sometimes referred to by the alternate name, *Clytia gregaria*. These are the same green fluorescent proteins.

The claimed protein has (1) about the same approximate molecular weight and (2) about same excitation and emission spectra as the green fluorescent protein of Levine.

The sequence of SEQ ID NO:2 is inherent in the isolated GFP protein of Levine.

Accordingly, Levine et al. anticipated the instant claim.

Tsien

Claims 1-4, 10-13 and 15-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US-5,777,079, published Jul. 7, 1998).

Claim 1 is directed to an isolated nucleic acid molecules selected from the group consisting of:

a) a nucleic acid molecule encoding a polypeptide having the amino acid sequence of SEQ ID NO:2;

b) a nucleic acid molecule comprising the sequence of SEQ ID NO:1;

c) a nucleic acid molecule which is at least 95% homologous to SEQ ID NO:1 whose complementary strand hybridizes under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1, and encodes a fluorescent protein.

The examiner interprets option c) of claim 1 as requiring (1) only a small region of the claimed nucleic acid molecule as being 95% homologous to SEQ ID NO:1; (2) the complementary strand of the nearly any nucleic acid molecule (especially those taught by Tsien which encode fluorescent proteins) as being able to hybridize under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1; and (3) the fluorescent proteins of Tsien (especially the mutant GFP which has an excitation peak of about 475 nm and an emission peak of about 493 nm) as encoding a fluorescent protein.

Tsien et al. teach modifications of green fluorescent protein having markedly different excitation and emission spectra from wild type GFP (abstract). Furthermore, Tsien et al. teach a mutant GFP which has an excitation peak of about 475 nm and an emission peak of about 493 nm (See Fig.3a and Fig.3b). Tsien et al. teach the nucleic acid sequence which encodes the mutant GFP. Furthermore, the complementary

strand of the Tsien nucleic acid would hybridize under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1. In addition, at least a portion of the Tsien mutant GFP is 95% homologous to SEQ ID NO:1, since the instant application teaches that the Tsien GFP is 44% homologous to the instantly claimed GFP. Additionally, the examiner interprets the phrase, "encodes a fluorescent protein" as referring to the nucleic acid molecule to which the claimed nucleic acid hybridizes (i.e., a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1). Optionally, the examiner can interpret the phrase "encodes a fluorescent protein" as referring to the nucleic acid molecule which encodes the GFP of Tsien.

As described above, Claim 15 is also anticipated by Tsien.

Tsien also teaches vectors (claims 3 and 11) comprising nucleic acids encoding mutant GFP; host cells (claim 4); promoters (claim 2); inducible promoters (claim 12); methods of using fusion proteins (claim 10); methods of producing a fluorescent protein (claims 13 and 16).

Therefore, Tsien et al. anticipated the instant claim.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner
Art Unit 1633